

REMARKS

Claim 1 is amended by incorporating the subject matter of claim 4 and claim 4 is canceled. Claim 11 is also amended in view of the amendment to claim 1.

Claims 18-19 and 29-31 are withdrawn from consideration.

No new matter is presented.

I. Restriction/Election

The Examiner has withdrawn 18-19 and 29-31 from consideration.

Applicants respectfully request rejoinder of claims directed to methods of making and methods of using the claimed product once the product claims are found allowable in accordance with the provisions of MPEP § 821.04.

II. Claim Rejection under 35 U.S.C. § 103

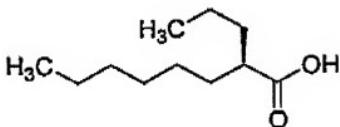
In paragraph 9 of the Office Action, claims 1-5, 7-16, 20-28 and 33-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hasegawa et al (Bull. Chem. Soc. Jpn 2000, 73, 423-428) or Hisao et al (JP 8-291106) in view of Ohuchida et al (US 6,201,021) and Black (US 6,043,223).

Applicants respectfully traverse the rejection.

The Examiner asserts that the present invention is obvious based on the combination of Hasegawa et al or Hisao et al in view of Ohuchida et al and Black. The Examiner relies on Black, which teaches the use of a phosphate buffered saline solution as a carrier for bradykinin and an infusion preparation of bradykinin that is dissolved in an aqueous solution containing sodium hydroxide and a phosphate buffered saline solution. However, Black is not related to the present invention and cannot be combined with the other cited references as suggested by the

Examiner. Thus, Applicants submit that Black is inappropriately cited and the rejection is improper.

Black relates to compositions and methods for increasing permeability of abnormal brain tissue to pharmaceutical agents. As indicated by the Examiner, Black discloses an aqueous composition comprising 10-40 µg/mL bradykinin and 0.09% phosphate buffered saline for carotid artery administration. However, bradykinin is a basic amino acid consisting of nine amino acids. Bradykinin has a structure of H-Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg-OH and its molecular weight is about 1060. On the other hand, (2R)-2-propyloctanoic acid in the present invention is a compound which has the following structure:



and its molecular weight is 186.

It cannot be said that the composition of the present invention is obvious based on the disclosure of a combination of Hasegawa et al or Hisao et al in view of Ohuchida et al and Black, which relates to an infusion preparation for a compound which has a much different molecular weight and different features of its liquid composition. Additionally, a person skilled in the art would not have been motivated to combine Black which describes a compound that has significantly different physicochemical properties (i.e., bradykinin is a basic compound while (2R)-2-propyloctanoic acid is an acidic compound) with a reasonable expectation of success. Namely, Black is inappropriately cited since it does not relate to the other cited references or the

claimed invention. Thus, the present invention cannot be said to be obvious based on a combination of the cited references, whether taken alone or in combination.

Further, even if Black could have been combined with Hasegawa et al or Hisao et al and Ohuchida et al, the present invention could not have been achieved. Specifically, at column 5, lines 51-59 of Black, the method of preparation of the composition for increasing permeability of agents is described as follows:

Zaprinast is not soluble directly in saline. Accordingly, it is preferred that the pharmaceutical solution be prepared by dissolving zaprinast in 1 M sodium hydroxide to form a concentrated solution of approximately 100 to 500 mg/ml zaprinast. This concentrated solution is then dissolved into phosphate buffered saline (PBS) to the final desired concentration. Bradykinin or the bradykinin analog is then added to the solution to form the final pharmaceutical preparation.

At column 5, lines 47-51 of Black, it is described that the concentration of bradykinin(bradykinin analog is adjusted to be 15 µg/mL to 50 mg/mL and the concentration of zaprinast is adjusted to be 2-15 mg/mL for intravenous administration.

From the description of Black, the composition for intravenous administration disclosed by Black is a preparation comprising:

- (a) 15 µg/mL to 50 mg/mL of bradykinin(bradykinin analog;
- (b) 2-15 mg/mL of zaprinast;
- (c) 4-150 mM NaOH derived from NaOH used for dissolution for zaprinast; and
- (d) 0.09% PBS.

In this connection, the molecular weight of bradykinin is 1060. Therefore, the concentration described in (a) above is 0.014 - 47.17 mM in molar concentration. Additionally, the basic metal ion concentration included in 0.09% PBS is 0.016 mM and does not change.

When bradykinin and the basic metal ion are converted to equivalents as recited in amended claim 1, the preparation of Black would be a preparation comprising about 0.085 - 10715 equivalents of the basic metal ion based on 1 equivalent of bradykinin. Therefore, based on the equivalent number, the range of equivalents of the basic metal ion is very broad and more than 120,000 times of basic metal ion can be included in comparison with bradykinin.

On the other hand, the problems of clouding and difficulty in preservation of (2R)-2-propyloctanoic acid and salts thereof can be solved by the present invention allowing for the coexistence of the basic metal ion in an amount of a narrow range of about 1 to 5 equivalents based on 1 equivalent of (2R)-2-propyloctanoic acid. Namely, one of ordinary skill in the art would not have had a reasonable expectation of success in solving the problems of clouding and difficulty in preservation using only 5 equivalents based on the range of more than 120,000 times that of the active ingredient as described in Black. Further, Black does not mention or even recognize the problems addressed by the present invention.

Furthermore, the problems of clouding and difficulty in preservation of (2R)-2-propyloctanoic acid and salts thereof are solved by the present invention by changing the amount of the basic metal ion according to the active ingredient. However, in Black, a predetermined amount of the basic ion metal is used as a carrier for any concentration of active ingredients. Therefore, the technical feature of Black is totally different from that of the present invention.

Moreover, the reason for adding NaOH in Black is that zaprinast cannot be dissolved in saline. As described above, since the reason for the addition of the basic metal ion in the present invention is to solve the problem of clouding and difficulty in preservation, the technical features are also different.

For the reasons set forth above, Black is inappropriately cited by the Examiner and there is no apparent reason to combine the references as suggested. Accordingly, the present invention is not rendered obvious.

Reconsideration and withdrawal of the rejection is respectfully requested.

III. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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